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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/082,112	05/20/98	MENDOZA	A	MSU4.1-406

HM12/1107

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EXAMINER	
TURNER,S	
ART UNIT	**PAPER NUMBER**
1647	23

DATE MAILED: 11/07/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/082,112	Mendoza
Examiner	**Group Art Unit**
Sharon L. Turner, Ph.D.	1647

☒ Responsive to communication(s) filed on 6-30-00

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 16-25 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 16-25 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Amendment

1. The Art Unit of U.S. Patent application SN 09/134,312 has changed. In order to expedite the correlation of papers with the application please direct all future correspondence to Examiner Turner, Technology Center 1600, Art Unit 1647.

2. Upon further consideration, the finality of the previous office action is withdrawn. It is noted that a Notice of Appeal and Appeal Brief have been filed. Applicant can request a refund for the associated fees or leave it as credit for future appeals.

3. As a result of applicants amendment, all rejections not reiterated herein have been withdrawn by the examiner.

4. The amendment filed 3-14-00 has been entered into the record and has been fully considered.

5. Claims 26 and 27 have been canceled. Claims 16-25 are pending.

6. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Rejections

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. The amendment filed 10-17-99 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: ATCC 74446.

Applicant is required to cancel the new matter in the reply to this Office action.

9. Claim 21 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. Amendment of claim 21 removes ATCC 58643 and replaces it with ATCC 74446. Applicants submit support in the Appeal Brief filed 6-30-00 that indicates that ATCC 74446 is a resubmission of ATCC 58643. However, there is no evidence of record that the deposited strains are the same. Thus, in the absence of assurances of the deposited material such recitation constitutes new matter.

10. Claim 21 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification lacks complete deposit information for the deposit of ATCC 74446. Because it is not clear that cell lines possessing the properties of ATCC 74446 are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the claims require the use of ATCC 74446, a suitable deposit for patent purposes is

required. Accordingly, filing of evidence of the reproducible production of the cell line claimed in claim 21 is required. Without publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of the cell line is an unpredictable event.

Applicant's referral to the deposit of ATCC 74446 throughout the specification is an insufficient assurance that all required deposits have been made and all the conditions of 37 CFR § 1.801-1.809 have been met.

If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of the patent on this application. These requirements are necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of deposit and the complete name and full street address of the depository is required.

If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR § 1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

© the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non replicable.

In addition, a deposit of biological material that is capable of self-replication either directly or indirectly must be viable at the time of deposit and during the term of deposit. Viability may be tested by the depository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of a biological material not made under the Budapest Treaty must be filed in the application and must contain:

1) The name and address of the depository;
2) The name and address of the depositor;
3) The date of deposit;
4) The identity of the deposit and the accession number given by the depository;
5) The date of the viability test;
6) The procedures used to obtain a sample if the test is not done by the depository; and
7) A statement that the deposit is capable of reproduction.

As a means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the ATCC 74446 cell line described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundack, 773F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR § 1.801-1.809 for further information concerning deposit practice.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 16-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mendoza et al, J. Mycol. Med, 1996, 6:151-164, Mendoza et al, Mycopathologica, 1992(a), 119:89-93, (IDS: Ref. AI), Mendoza et al, J. Clin. Microbiology, Nov. 1992(b), p. 2980-83, Panella et al, Cancer Res., 50(14):4429-35, Sigma Catalog, p.1874, 1992 and Amicon Catalog, p. 35, 1993.

Mendoza et al, 1992(a) teach two vaccines for Pythiosis. The first, page 90, column 2, Vaccine production, comprises inoculation and growth of *P. insidiosum* in Sabouraud dextrose broth, followed by filtration through a Whatman No. 40 filter paper. The fungal mass was then washed three times with 200 ml of 0.75% of NaCl solution. In the last wash, the cell-mass was resuspended in 15 ml of sterile saline solution and then broken in a Braum MSK cell homogenizer, until microscopically 80% of the hyphae were observed to have been fragmented. This step effectively separates and releases the intracellular and extracellular proteins produced inside the cell from the cell material, and thus provides an admixture of intracellular and extracellular proteins. The hyphae were transferred to a container, desiccated and the final dose was adjusted to 5 mg dry weight/ml with 5% phenolized, sterile saline (an aqueous) solution. Homogenization breaks the cells open and is inherently deemed to be no different from sonication. As described on page 89, column 1, line 12 Introduction, Mendoza et al., have found that nine Pythium strains isolated from humans, horses and dogs with active pythiosis belonged to the same species, teaching that *P. insidiosum* is inherently equivalent to ATCC 7446 and 58643. *P. insidiosum* was also used in the production of the CMV vaccine, page 90, Vaccine

production. The CMV procedure utilizes centrifugation for the cell washes. The beneficial results of the CMV vaccine are illustrated in Tables 1-3.

In addition to the CMV vaccine, the SCAV vaccine is prepared by growth in Sabouraud dextrose broth for 5 days, the cultures are then killed with phenol (0.5% final concentration), (an equivalent reagent to thimerosol, see Merthiolate, J. Clin. Microbiol., Nov. 1992, p. 2980-83 (AJ)), and then concentrated 20-fold in a stir cell. The concentrated soluble antigen obtained from each flask is precipitated with 50 ml of chilled acetone twice and centrifuged at 10,000Xg. The supernatant is drained and the precipitated antigen is resuspended in 25 ml 0.75% NaCl sterile solution, see p. 90, col. 2, line 33-p.91, col. 1, line 8. This preparation thus comprises mixed intracellular and mixed extracelluar proteins. Vaccination and results from vaccination are shown in Figures 1, 2, and 4. Both vaccines are administered to mammals subcutaneously, see, p. 91, col. 1, lines 16-20.

The second method (SACV) of vaccine preparation disclosed in Mendoza et al 1992(a) comprises the use of cultured filtrate antigens prepared by growth of *P. insidiosum*, subsequent killing of the cells with phenol (an equivalent reagent to thimerosol), and concentration by 20-fold in a stir cell (Amicon Corp.) The concentrated soluble antigens were precipitated with 50 ml chilled acetone twice and centrifuged at 10,000 X g (an equivalent step to dialysis). The supernatant was drained and the precipitated antigen was resuspended in 25 ml of .75% NaCl sterile solution. As set forth Mendoza et al 1992(a), teaches the effectiveness of the SACV vaccine in Tables 1-2 and 4.

The benefits of mixed intracellular and extracellular protein vaccines are disclosed in Mendoza et al, Mycopathologica, 1992(a), 119:89-93, (IDS: Ref. AI) or Mendoza et al, J. Mycol. Med, 1996, 6:151-164 are set forth above. These vaccines however are not produced by the process steps outlined, wherein the admixed proteins are *dialyzed* to remove low molecular weight components less than 10,000 MW.

Mendoza et al, J. Clin. Microbiology, Nov. 1992, p. 2980-83 teach the alternative preparation of antigens from *P. insidiosum*, wherein the cells are killed with Merthiolate™, the trademark name for thimerosol, (Sodium ethyl-mercurithiosalicylate; Mercury[(o-carboxypphenyl)thio]ethyl sodium salt, see Sigma Catalog, 1992), and followed by ultrafiltration under positive pressure in a stirred cell fitted with a PM-10 membrane (Amicon Corp., Lexington, Mass.) for the purpose of removing low molecular weight materials. These steps kill the cells, and remove the thimerosol from the vaccine.

Thimerosol has been shown to exhibit effects on the immune response which are independent of the administered antigens, see for example Panella et al which teach the benefit of thimerosol as an antigenic preservative and the benefit of subsequent removal by *dialysis* to eliminate nonspecific immune effects of the ethyl-mercury (in favor of the antigens being tested). Thus, the only difference between the claimed vaccine preparation and that of the prior art is the removal of low molecular weight components via *dialysis* in contrast to the prior art method of centrifugation through a PM-10 membrane. Dialysis removes small molecules under 2,000-12,400 molecular weight but would not remove extracellular and intracellular proteins greater

than approximately 10,000 MW which are protective. Thus, as disclosed by Panella et al., it would have been prima facie obvious to one of skill in the art (knowing the presence of protective high MW intracellular and extracellular proteins from P. insidiosum), to modify the killing step using thimerosal (an antigenic preservative) and centrifugation through a PM-10 membrane, with a killing step using thimerosal and subsequent dialysis, to produce an antigenic composition with the immunogenic properties of the claimed invention. The skilled artisan would be motivated to use dialysis given the benefit of thimerosol as an antigenic preservative and the benefit of subsequent removal by *dialysis* to eliminate nonspecific immune effects of the ethyl-mercury (in favor of the antigens being tested) as taught by Panella et al. One of skill in the art would be further motivated to use dialysis as a method of removing low molecular weight molecules over PM-10 membrane centrifugation given that dialysis tubing is cheaper than PM-10 membranes, see in particular Sigma Catalog p. 1874 and Amicon Catalog p. 35. One of skill in the art would thus have been motivated to use the claimed steps to provide antigenic preparations based on the teachings of Panella et al of the preservative properties of thimerosol and the ability to remove the ethyl-mercury by dialysis while retaining high molecular weight protective antigens, the benefits of such method in eliminating non-specific immune responses and further the economic advantage of using cheaper dialysis tubing for the removal of low molecular weight components. One of skill in the art would have expected at least equivalent results with such a preparation due to the killing and preservation of P. insidiosum antigenic epitopes via thimerosol,

and the elimination of nonspecific immune stimulation by ethyl-mercury removal using dialysis. Thus, for these reasons the prior art teachings render the claimed invention obvious.

Claims 16-17 recite a method for treatment of Pythiosis in humans. Mendoza et al, 1996 teach the prevalence of human pythiosis infection and a need for effective human vaccines, page 156, column 2. Mendoza et al, 1996, also teach the benefits of vaccination using antigens derived from *P. insidiosum*, see page 158, column 1, lines 5-8, 24 and Immunotherapy, page 161-162 with reference to the vaccine treatments of IDS:References AB, AC, AD, AH, AI and AJ including the CMV and SCAV vaccines, see in particular references and procedures as set forth above. Mendoza et al, 1996, teach that the addition of cytoplasmic antigens, containing the 28K, 30K and 32K immunodominant proteins to these pythium vaccines (in reference to Mendoza, Enhancement of the therapeutic effect of a vaccine against equine pythiosis insidiosis by a hyphal antigen protein of the oomycete *Pythium insidiosum,* The Third NIAID Workshop in Medical Mycology Series. Montana, September, p.9, 1995) enhances curative properties, page 159, line 15-18. Mendoza et al teach similarilties in the recognition of Pythium antigens detected from sera of humans and horses infected with *Pythiosis insidiosum*, see page 159, Immunodiffusion test and Western Blot. Mendoza et al, 1996, however do not teach the benefit of such vaccine preparations in humans. Knowing the similarity in antigenicity and serological reactivity in humans to that found in horses, and the benefit of the described vaccines in horses, it would have been prima facie obvious to use the vaccine antigen preparations described to treat *P. insidiosum* in humans. One of skill in the art would have been motivated to do so based on the effectiveness

of the vaccine in horses, a knowledge of the similarity in mammalian immune function, the similarities in antigens and recognition by sera antibodies in humans and horses, and the need for effective treatments of such infections in humans as taught by Mendoza et al., 1996. Thus, the reference teachings render claims 16-17 obvious.

Status of Claims

13. No claims are allowed.

Conclusion

14. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
November 6, 2000

NITA MINNIFIELD
PRIMARY EXAMINER